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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,719	09/20/2002	James Robl	P 280713	2839

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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,719	ROBL ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *18-31 and 46-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 32-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application filed September 20, 2002, is a 371 national stage filing of PCT/US00/25090, filed September 14, 2000.

Claim 1-50 are pending.

Election/Restrictions

Applicant's election with traverse of Group II in the reply filed on July 22, 2005 is acknowledged. The traversal is on the ground(s) that it would not be an undue burden to search groups I and II together. Applicants' arguments are found persuasive because to practice group II, one must be able to practice the methodology of group I, or alternatively should be able to more simply practice the methodology where no genetic manipulation is required. Groups I and II are rejoined. Applicants do not traverse the restriction of other groups, and the restriction requirement of these groups is maintained for the reasons of record.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-50 are pending. Claims 18-31, 46-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on July 22, 2005. Claims 1-17, 32-45, drawn to a method of producing an unmodified and modified embryonic or stem cell is under examination.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specifically, review of the instant specification identifies multiple citations of references, however no IDS has been submitted with the instant application.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-17, 32-45 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 4-11, 13-19, 24-30, 32-38, 40-52, 58-60 of copending Application No. 09/260,468. Although the conflicting claims are not identical, they are not patentably distinct from each other because each are directed to nuclear transfer methodology encompassing the use of mammalian donor and recipient cells to produce embryonic stem cells.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-17, 32-45 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-58 of copending Application No. 09/467,076. Although the conflicting claims are not identical, they are not patentably distinct from each other because '076 clams the mammalian species of ungulate which would anticipate the genus of any mammal instantly claimed. Again, each are directed to nuclear transfer methodology encompassing the use of mammalian donor and recipient cells to produce embryonic stem cells.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-17, 32-45 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17, 32-45, 51-57, 62-75 of copending Application No. 10/329,979. Although the conflicting claims are not identical, they are not patentably distinct from each other because each are directed to nuclear transfer methodology encompassing the use of mammalian donor and recipient cells to produce embryonic stem cells. It is noted that dependent claims set forth embodiments that mirror exactly the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17, 32-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing mouse and human embryonic stem like cells comprising the use of nuclear transfer methodology where in a donor cell and an oocyte of the same species is used, does not reasonably provide enablement for methodology encompassing any other mammalian species nor cross species nuclear transfer methodology. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Three issues are the focus of the enablement rejection: first, the ability to obtain and culture stem cells from any species of mammal; second, the breadth of the claim as it is directed to cross species nuclear transfer, and finally; the ability to selectively alter any specific gene, or more specifically to inhibit a function such as differentiation into a specific lineage (claim 36) or apoptosis (claim 43). In support of the rejection Examiner cites Wolfe et al. (Theriogenology, 3341):350, 1990) who teach that the affects of intergeneric nuclear transplantation was studied and that species more distant from the cow were less capable of supporting growth and differentiation of the resulting NT unit, and more broadly reviewed by Gurdon (J. Cell Sci 4:287-

318, 1986) who teaches that species as distant as human and Xenopus have been tested by nuclear transfer and while capable of supporting several cell divisions, is always lethal usually arresting at an irregular blastulae (page 300). While Wolfe et al. and Gurdon do not specifically teach what causes the arrest in development, Meirelles et al. (Genetics 158:351-356) teach that while mitochondrial heteroplasmy may occur in systems with related nuclear and mitochondrial DNA, even unrelated species of Bovus do not support the full development of a nuclear transfer unit generated by more distant species. A more recent review by Dominko et al. (Biol of Reprod 60:1496-1502, 1999) provides a even more generally review for the use of distant mammalian species clearly teaching the necessity of testing the compatibilities of cytoplasmic (i.e. mtDNA) and nuclear DNA when practicing interspecies NT (see summary on page 1501). Therefore, based on the art of record only species with closely related nuclear and cytoplasmic genes would be capable of successfully reconstituting the genetic complement necessary for development of an embryo (see surmmary in abstract). Moreover, the simple reliance of the instant specification on nuclear transfer methodology known in the art fails to address even such limitations of successfully practicing intra-species nuclear transfer (see for example Aronson et al. (Current Topics in Devolopmental Biology 23: 55-71). Moreover, the art teaches that embryonic stem cells from the broad range of animals encompassed by the instant claims encompassed by the claims have not been successfully isolated from normal embryos. The present specification provides no further guidance providing the necessary methodology required to isolate embryonic stem cells beyond those readily known in the art. In summary, while the methods of inserting the nuclear material from one species into the oocyte of another different species was known and practiced at the time of the claimed invention, the methodology to successfully culture the

resulting NT unit into a blastocyst from which ES cells could be obtained was not successfully practiced. The instant specification relies in great part on the teaching in the art to practice nuclear transfer methodology and fails to address art recognized shortcomings for successfully culturing transpecies NT unit cells from distantly related species. Further, lacking the ability to obtain a viable NT unit capable of forming a viable embryo containing embryonic stem cells, the specification fails to provide the necessary guidance to isolate and culture embryonic stem cells from species from which embryonic stem cells have not been derived. With respect to the working examples provided in the present specification for cell culture obtained from introducing human nuclear material into a cow embryo, as indicated in the previous office action the morphological characterization of the resulting cells is insufficient to establish that the cells are in fact embryonic stem cells. Consistent with this view subsequent peered reviewed articles have questioned the lack of substantive data support for the instant claims (Science 282:1390-1391, 1998).

Generally, the claims are directed to a method for the production of human or mammalian embryonic or stem-like cells comprising; inserting a differentiated human or mammalian cell or nucleus into an enucleated oocyte from a different animal species than the human or mammalian cell forming a NT unit; activating the NT unit; inserting cytoplasm into the oocyte from the same species of animal as the donor cell or nucleus; culturing the activated NT unit into cells; and culturing the cells to obtain embryonic or stem-like cells. As noted above, the claims further include embodiments of genetically modifying the resulting embryonic or stem-like cells. The specification while providing the literal support for such embodiments, fails to provide the necessary guidance for affecting the methods. The claims require that a cell

be cultured to obtain a cell in which recombination has occurred, and importantly will still serve as a donor cell that can successfully be used in NT technology. The specification fails to provide the necessary guidance wherein the resulting primary cell routinely undergoes recombination commensurate in scope with the claims. Further, dependent claims require the expression of particular genes and/or a consequential functions, however beyond the recitation of various genes, there is no specific guidance on affecting these method steps for the scope of the claims. Importantly, with the given technology on which the instant specification depends, the artisan would not be able to reproducibly provide a donor cell with the correct karyotype and resulting functional attributes that could be routinely and successfully used as a donor cell. The specification discloses the preparation of nuclear transfer units using a method of nuclear transfer of adult human epithelial cell nuclei into enucleated bovine oocyte to form a nuclear transfer (NT) unit by electrofusion techniques. The method disclosed in Example 1 of the specification result in the production of a NT unit (16-400 cell stage) according to Table 1, page 63. Although the methods of the instant invention result in the production of a NT unit of which Applicants report propagates into what appears to be ES-like cell colonies (as determined by cell morphology); Applicants fail to demonstrate that the ES-like cells function as true ES-cells in that they are in fact totipotent or that they function as stem cells in that they are capable of differentiation into other multilineage cell-types. As such, Applicants fail to enable the production of embryonic or stem-like cells. Again, the unpredictability of the method of NT transfer, as a whole, lies in the need to convert a differentiated cell to a totipotent cell (embryonic stem cell). Cells contain the same DNA complement, however, in differentiated tissues, not all DNA sequences are expressed. For example, a liver does not make rhodopsin and retinal cell

structures, and retinal cells do not make clotting factors and hepatocyte structures. For a cell to go through all the steps of development, it, or its nucleus, must be reverted to the stage where all DNA sequences can potentially be expressed, and expression regulated according to developmental stage. Applicants have not provided evidence that the cells produced by their methods are true pluripotent cells (embryonic stem cells or embryonic or stem-like cells). Applicants fail to demonstrate whether their ES-like cells stain positive for alkaline phosphatase (AP), exhibit the formation of embryoid bodies, spontaneously differentiate into at least two different cell type, or express ES cell markers. Applicants only disclose several morphological characteristics (Example I, page 62).

Therefore, in view of art of record it would have required undue experimentation to determine the parameters listed above, the lack of direction and/or guidance provided by the specification, the absence of working examples for the demonstration of or reasonable correlation to producing human or mammalian embryonic or stem-like cells capable of mere differentiation, for example, the unpredictability and undeveloped state to the art with respect to cross species nuclear transfer (using adult differentiated nuclei) for production of embryonic stem cells which give rise to germline tissue and the whole animal or which may be induced to differentiate, in particular with respect to carrying out a process involving insertion of differentiated, adult human cell nuclei into bovine oocytes, the unpredictable state of the art with respect to extrapolating results obtained from ES cells of different species of animals to results obtained from chimeric bovine/human embryonic or stem-like cells.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. 27 USPQ2d 1662 *Ex parte Maizel*. Scope of Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). In view of the quantity of experimentation necessary to determine the parameters listed above, the lack of direction or guidance provided by the specification, the absence of working examples for any other species, and the general unpredictable state of the art, it would have required undue experimentation for one skilled in the art to practice the claimed inventions as broadly claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolfe *et al.* (Theriogenology, 1990), Collas *et al.* (Molecular Reproduction and Development, 1994) and Westhusian *et al.* (Theriogenology, 1996).

The claims are directed to a method of producing embryonic or stem-like cells via nuclear transfer of a differentiated human or mammalian cell nucleus to an animal oocyte, in particular for the use of human cells. To the extent that the prior art teaches and provides the same guidance as the instant specification it is set forth that Wolfe *et al.* teach a method of cross-species nuclear transfer using nuclei from bovine preimplantation embryos and oocytes of a varying species. Wolfe *et al.* disclose the production of blastocysts derived from bovine nuclei and bison ovum as well as bovine nuclei and goat ovum. Thus, the experimentation of Wolfe *et al.* demonstrates that mammalian nuclei may be capable of interacting with cytoplasm from other mammalian species to support normal development (see summary in Abstract). Wolfe *et al.* do not propose nuclear transfer of human or mammalian differentiated nuclei into bovine oocytes, however, at the time the claimed invention was made, Collas *et al.* disclose results indicating that transplanted differentiated nuclei may be pluripotent. Collas *et al.* also suggest that "a variety of differentiated mammalian cell types may promote early preimplantation development of NT embryos." (page 266, Discussion section). Accordingly, in view of the collective cited prior art, it would have been *prima facie* obvious for one of ordinary skill in the art to select human or mammalian differentiated cell nuclei and animal oocytes of a varying species for use in nuclear transfer with a reasonable expectation of producing at least one nuclear transfer unit of which is capable of being cultured into cells which meet the limitation of "embryonic or stem-like" cells.

Further, at the time of the claimed invention, it was recognized that the various methods for nuclear transfer had technical drawbacks which reduced the efficiency of the methodology. Westhusin *et al.* teach that one such limitation occurs during the process of enucleating the oocyte when ovum cytoplasm is removed (page 244; fourth column). Further, Westhusin *et al.* note that their experiments and those of others clearly indicate that the cytoplasm/nuclear ratio plays an important role in embryonic development, where reduced levels of cytoplasm results in a significant effect on embryo survival (page 244; first column). In view of their results and that reported by others, Westhusin *et al.* conclude that a reduction in the amount of cytoplasm affects the number of cells in the morula and blastocyst, affects embryo quality, and may affect later embryo development (page 248; beginning of discussion section). Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to control the amount of cytoplasm during the procedure of nuclear transfer. As noted by Westhusin *et al.* many of the nuclear transfer procedures result in the loss of cytoplasm, so one of ordinary skill in the art would have been motivated, in view to the work of Westhusin *et al.* to include the addition of cytoplasm to the NT unit. In addition, it is also noted that the cytoplasm/nuclear ratio is an important factor in the survivability of the embryo, thus, the artisan would have been further motivated to control the cytoplasm/nuclear ratio by the addition of cytoplasm during the nuclear transfer procedure which was lost during enucleation. There would have been a reasonable expectation of success given the state of art and that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. 103, all that is required is a reasonable expectation of success. See *In re O'Farrell* 7USPQ2d 1673 (CAFC 1988).

Thus, the claimed invention, as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach

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